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A CASE OF SMALL CELL CARCINOMA OF THE KIDNEY

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A 47-year-old man had a retroperitoneal tumor measuring 18 cm in maximum diameter of the left kidney that was diagnosed with computed tomography (CT)-guided needle biopsy as small cell carcinoma. Microscopically, the tumor cells showed immunohistochemical reaction for neural cell adhesion molecule antibodies. This patient with advanced renal small cell carcinoma and multiple metastatic lesions was treated with the first-line combination chemotherapy of cisplatin, etoposide and ifosphamide, which showed a partial response of primary renal tumor and a complete response of liver metastasis, and with the second-line chemotherapy of cisplatin and irinotecan, which showed a complete response of Virchow's nodal metastasis. Thereafter, in spite of salvage chemotherapy of amurubicin hydrochloride for persistent and refractory renal small cell carcinoma, he died 32 months after the first presentation due to local progression. However, combination chemotherapy of these anticancer agents made his prognosis more favorable than we expected before treatment.

The extrapulmonary small cell carcinomas are generally known to be more aggressive and malignant than the lung small cell carcinomas, and small cell carcinoma arising from the kidney is an extremely rare malignant neoplasm, with only 34 cases reported in the English or Japanese literature. The prognosis of renal small cell carcinomas is currently limited as compared with the lung small cell carcinomas, and therefore a cumulative investigation of a larger number of cases treated with multidisciplinary modalities including combination chemotherapy is necessary.

(Hinyokika Kiyo **53** : 235–240, 2007)

Key words : Small cell carcinoma, Kidney, Combination chemotherapy

INTRODUCTION

Although small cell carcinoma originating from extrapulmonary sites is reportedly increasing in the database service, renal small cell carcinoma is extremely rare. We encountered a patient with small cell carcinoma involving multiple distant and lymph node metastases, and he was treated with combination chemotherapy, radio-surgery and palliative therapy for elongation of the survival time. Herein, we describe the clinical course of our patient and reviewed the 34 cases of renal small cell carcinoma reported in the English or Japanese literature including our present case.

CASE REPORT

A 47-year-old man was referred to our department complaining of left back pain and anorexia persisting for 2 years. A contrast-enhanced magnetic resonance imaging (MRI) revealed a retroperitoneal tumor measuring 18×11×10 cm in diameter that displaced the upper pole of his left kidney (Fig. 1a) with liver metastasis and the costal metastasis. A contrast-enhanced computed tomography (CT) scanning was additionally performed to definitely diagnose the renal tumor and multiple liver metastases (Fig. 1b). The renal tumor showed irregular margin and heterogeneous weak enhancement. Extension to the spleen, left side of the diaphragm, and para-aortic region over the midline was observed, but there was no tumor thrombus in the left renal vein or inferior vena cava. Thoracic computed tomography (CT) revealed metastasis in Virchow's subclavian lymph node (Fig. 1c), but there was no evidence of any broncho-pulmonary tumor. The laboratory examinations including tumor markers revealed normal findings except elevated LDH (961 IU/l; normal range: 116-231 IU/l) and neuron specific enolase (100 ng/ml; normal range: <10 ng/ml).

CT-guided needle biopsy of the renal tumor was performed, and histopathological staining with hematoxylin & eosin revealed honeycomb proliferation of small cells with hyperchromatic nuclei and scanty cytoplasm (Fig. 2). Immunohistochemically, the tumor cells demonstrated negative staining for cytokeratin and chromogranin A, weakly positive staining for synaptophysin, and strongly positive staining for neural cell adhesion molecule. Thus, this tumor was diagnosed as primary renal small cell carcinoma with evidence of cellular neuroendocrine function.

After 5 cycles of the first-line combination chemotherapy (every 3 weeks) consisting of cisplatin (80 mg/m^2 on day 1), etoposide (100 mg/m^2 on days 1–3), and ifosphamide (3,000 mg/m^2 on day 1), the neuron specific enolase and LDH levels showed normalization, and MRI showed 95% volume reduction of the renal tumor (Fig. 3a), a complete response of the liver metastasis (Fig. 3b) and costal metastasis, and 50% volume

Fig. 1. A Gadolinium-enhanced T1-weighted MRI revealed a renal small cell carcinoma measuring 18 × 11 × 10 cm in diameter that displaced the upper pole of his left kidney (a). Abdominal CT and thoracic CT revealed multiple liver metastases (b) and metastasis in Virchow's subclavian lymph node (c), respectively.

reduction of Virchow's lymph node (Fig. 3c). Two months later, the tumor showed progression and second-line chemotherapy with cisplatin (40 mg/m^2 on day 1) plus ilinotecan (40 mg/m^2 on days 1, 8, 15) was administered. After 6 cycles of the second-line chemotherapy (every 3 weeks), MRI and CT showed a minor response of the renal tumor and a complete response of the Virchow's lymph node metastatic lesions, respectively. The third-line salvage chemotherapy with amurubicin hydrochloride (45 mg/m^2 on days 1–3, every

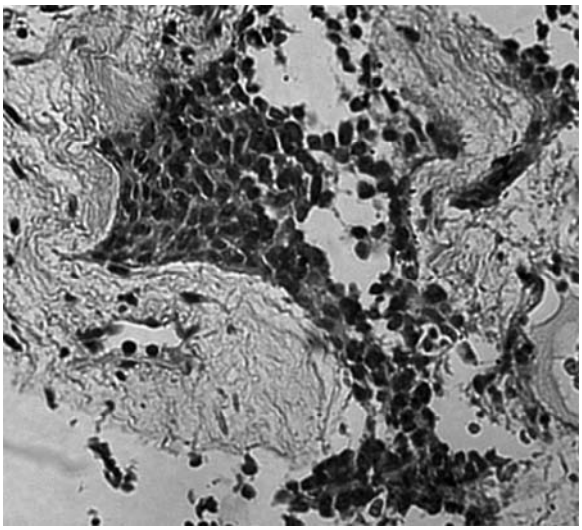

Fig. 2. Microscopical examination of needle biopsy showed honeycomb proliferation of small rounded tumor cells with high nucleus-cytoplasm ratio (hematoxylin & eosin : ×400).

3 weeks) for the persisting refractory renal tumor was administered. After 2 cycles of chemotherapy with volume reduction of the renal tumor, brain CT scanning demonstrated cerebral metastasis, which was treated with radio-surgery using γ-ray knife following craniotomy. After administration of another cycle of chemotherapy with amurubicin hydrochloride, the patient could not receive further treatment due to deterioration of his systemic condition, and finally he died of rapid progression of the primary lesion 32 months after the first presentation.

DISCUSSION

Small cell carcinoma mainly originates from the pulmonary region with highly malignant potential and represents its aggressive clinical course with early dissemination and frequent recurrence. The primary extrapulmonary small cell carcinomas account for 2.5–4.0% of all small cell carcinomas[1,2]. The extrapulmonary small cell carcinoma has been recognized as a clinicopathological entity with biological behavior and prognosis distinct from the lung small cell carcinoma. Primary extrapulmonary small cell carcinomas have been described in all sites of the body except in the central nervous system and liver[1], but small cell carcinomas arising in the kidney are very rare. Since most of the small cell carcinomas arising in the kidney are extensive and invasive at the first presentation, it is difficult to determine whether the primary site is the renal pelvis or renal parenchyma in many cases. The ratio of men to women is reportedly about 1 to 2. Galanis *et al.*[3] suggested some correlation between smoking and the extrapulmonary small cell carcinomas as there was a smoking history in 63% of the extrapulmonary small cell carcinomas in comparison to 72% of the lung small cell carcinomas.

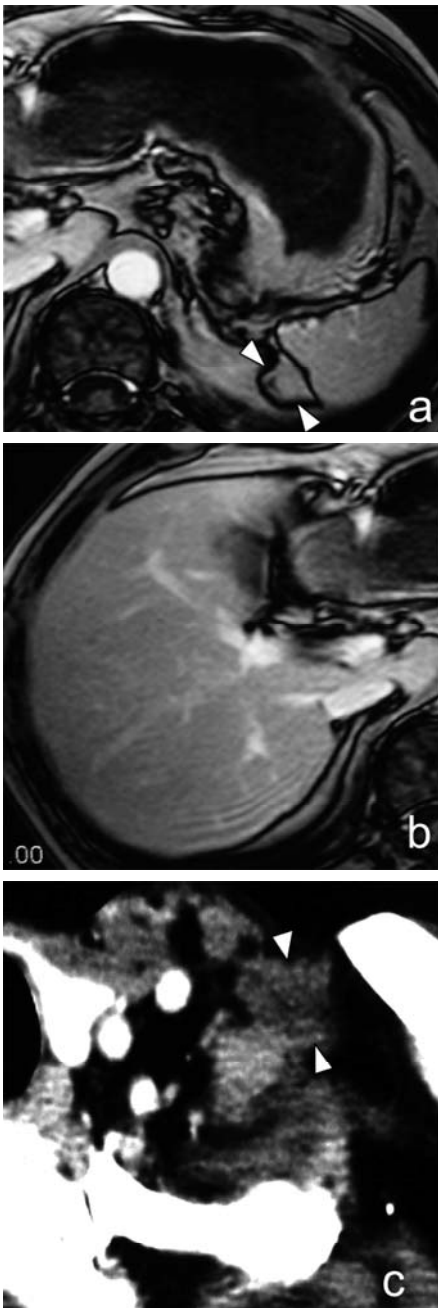

Fig. 3. After 5 cycles of the first-line combination chemotherapy consisting of cisplatin, etoposide, and ifosphamide, MRI showed 95% volume reduction of the renal tumor (a) and a complete response of the liver metastases (b), and thoracic CT showed 50% volume reduction of Virchow's lymph node (c).

Small cell carcinoma is generally diagnosed by the following histopathological characteristics : (1) small, ovoid to spindle-shaped cells, (2) hyperchromatic nuclei, (3) inconspicuous nucleoli, (4) scanty cytoplasm, and (5) unclear borderline between the individual cells. Because of the biological neuroendocrine features, the immunohistochemical tests for neuroendocrine markers, such as synaptophysin, chromogranin A, and neural cell adhesion molecule, are important and useful in the differential diagnosis from malignant lymphoma, sarcomas, and primitive neuroectodermal tumor[4,5]. Adenocarcinoma, transitional cell carcinoma, squamous cell carcinoma, or other undifferentiated carcinoma may occasionally coexist with small cell carcinoma according to the primary sites[6]. Christopher et al.[7] suggested that small cell carcinomas are derived from totipotent stem cells which can result in neuroendocrine and epithelial differentiation with malignancy.

To our knowledge, 34 small cell carcinomas of the kidney including our case have been reported in the English or Japanese literature[6–13], and their characteristics are summarized in Table 1. The median survival

Table 1. A summary of 34 patients with small cell carcinoma of the kidney

Mean age (yrs)	56.7±16.9 (range : 18–83)
Men/Women	13/21
Right/Left (unknown)	15/12 (7)
Mean size of 18 informative tumors (cm)	11.1±4.7 (range : 4–20)
Metastasis at initial diagnosis (total number of patients with each metastatic site shown below) (16 informative patients)	
Lymph nodes	13
Bone	4
Liver	3
Brain	2
Skin	1
Lung	1
Spleen	1
Surgery for primary tumor	
Nephrectomy	26
Partial nephrectomy	1
Biopsy only	7
First-line chemotherapy (20 patients)	
PE	6
IPE	1
VCPE (+A)	2 (1)
MV (or VCR) AC	2
AD	2
TP	1
CT	1
Others	5
Radiation therapy (7 patients)	
Primary tumor	2
Metastatic tumor	5
Prognosis	
Cancer death	20
Alive with disease	7
Alive without disease	5
Not described	2
Median survival period of cancer-death patients (mos.)	6.5 (range : 1–32)

* PE : cisplatin + etoposide ; IPE : ifosphamide + cisplatin + etoposide ; VCPE (+A) : vincristine + cyclophosphamide + cisplatin + etoposide (+ doxorubicin) ; MV (or VCR) AC : methotrexate + vinblastine (or vincristine) + doxorubicin + cisplatin ; AD : doxorubicin + dacarbazine ; TP : paclitaxel + cisplatin ; CT : carboplatin + teniposide.

period of 20 patients who died from small cell carcinoma was 6.5 (mean : 7.8±7.2 ; range : 1–32) months, which is poorer than that of the lung small cell carcinoma as previously reported[14]. In this review, 19 (56%) out of 34 patients with renal small cell carcinoma had metastatic lesions at the first presentation, and small cell carcinomas tended to metastasize to the lymph nodes, liver, or bone in the 16 site-informative patients as shown in Table 1. The median survival periods of cancer-death patients treated with chemotherapy (n＝9) and without chemotherapy(n＝11) were 5 (mean : 4.9±3.1 ; range : 1–10) and 8 (mean : 10.0±8.1 ; range : 2–32) months, respectively. There was a report that one patient achieved complete response in primary lesion and lymph node metastasis by chemotherapy with cisplatin and etoposide, and was alive without cancer for 96 months[15]. Our present case had a widespread primary site and metastases to the lymph nodes, liver and ribs, but persistent treatments could achieve survival prolongation for 32 months as suggested in a previous report[10].

Although small cell carcinoma is highly sensitive for radiation and chemotherapy, its prognosis is generally poor. Macky et al.[11] analyzed 180 cases of genito-urinary tract small cell carcinomas (106 in the urinary bladder, 60 in the prostate, 8 in the kidney, and 6 in the ureter) to elucidate the therapeutic outcomes or prognostic predictors, and they concluded that cisplatin-based chemotherapy for the bladder small cell carcinomas and primary surgical therapy for the prostatic small cell carcinomas are associated with favorable prognosis. Among the 34 cases reported previously, anticancer drugs and regimens were various and cisplatin and etoposide-based combination chemotherapy was most popular as shown in Table 1, but the optimal regimen was not determined for treatment of renal small cell carcinoma. The present case was very advanced small cell carcinoma of the kidney, and combination chemotherapy consisting of cisplatin, etoposide, and ifosphamide as employed for extensive lung small cell carcinoma was initiated as first-line chemotherapy. On the other hand, the cisplatin-based chemotherapies with etoposide and/or irinotecan achieved a significant volume reduction of the tumor and prolonged the survival in patients with pulmonary small cell carcinoma[16]. We likewise employed cisplatin and irinotecan as the second-line chemotherapy, and moreover, we administered a new agent, amurubicin hydrochloride, for the relapse after the second-line chemotherapy in consideration of the cisplatin-resistance of the tumor and cisplatin-induced adverse effects. Amurubicin hydrochloride is an anthracycline carcinostatic agent and has a strong anti-tumor effect on small cell carcinoma. Recently, clinical trials of amurubicin hydrochloride on patients with lung small cell carcinoma have suggested that amurubicin hydrochloride leads to better prognosis than the combination of cisplatin with etoposide or irinotecan[17].

CONCLUSIONS

Small cell carcinoma arising in the kidney is a very rare and malignant neoplasm, and little information is available regarding the therapeutic strategy. This report emphasizes that integration of several therapeutic modalities such as surgery, combination chemotherapy, and radiation, and cumulative analysis of the therapeutic outcomes are needed for improving the prognosis.

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和文抄録

腎原発小細胞癌の1例

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47歳，男性に左腎由来の最大径18 cmの後腹膜腫瘍を認め，CTガイド下針生検にて小細胞癌と診断した．組織診断で，腫瘍細胞は神経細胞接着分子抗体を用いた免疫染色に陽性であった．多発転移を伴う進行性腎小細胞癌の本患者は，cisplatin，etoposide，ifosphamideによるfirst-lineの多剤併用化学療法を施行され，腎原発巣のpartial responseと肝転移巣のcomplete responseを得た．さらに，cisplatinとirinotecanを用いたsecond-lineの化学療法にて，Virchowリンパ節転移巣のcomplete responseを得た．その後，執拗に残存し再燃する腎原発巣に対して，amurubicin hydrochlorideによるsalvage化学療法を施行したが，初診より32カ月後に局所進展のため癌死した．しかし，本症例については，これらの抗癌剤を用いた化学療法により，治療前に予想した以上に患者の予後は良好なものとなった．一般的に肺外小細胞癌は，肺小細胞癌よりも侵襲的で，より悪性度の高い腫瘍として知られている．その中でも，腎由来の小細胞癌はきわめて稀な悪性新生物であり，英文あるいは邦文論文報告も僅かに34件である．現況では，腎小細胞癌の予後は，肺小細胞癌の予後に比べて不良であり，何らかの多剤併用化学療法を含めた集学的治療による，より多くの症例での治療経験の集積とその調査が必要である．

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